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EXPERIMENTAL RESEARCHES ON SPECIFIC THERAPEUTICS.

BY

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LECTURE II.

On the Atreptic Function.

In my first lecture I dealt with the anchoring phenomena exhibited by the different kinds of parasitotropic substances, which thus aid the body in the process of recovery, and I chiefly discussed, in their historical sequence, the three therapeutically important agents, the antitoxins, the bacteriolysins and the opsonins of Wright. I, however, indicated that with these substances the possibilities were not yet exhausted. To-day I shall speak of a different series of processes which may aid the organism to fight its adversaries, processes of a more passive nature, in which a secretion of active attacking substances does not take place.

You will remember that in the early days of immunity the exhaustion theory played an important *rôle*. Chauveau thought that when the body overcomes an infection, there are removed from it certain substances necessary for the development of that particular bacterial species; should the same kind of bacteria again penetrate into an organism thus modified, they would not find those substances necessary for their growth, and thus a new infection could not occur. This theory has of late years, and especially since the discovery of the different kinds of anti-bodies, ceased to be of importance in practical medicine. In point of fact, it is hard to imagine that in the living body, as a result of some infectious disease, which need not have produced any serious disturbances, there should have occurred a final and permanent disappearance of certain chemical substances. That during disease the internal secretions should become disturbed, and that possibly at this time certain cellular products should be temporarily removed by excessive consumption and insufficient nutrition, is possible and even probable, but it is quite unintelligible how, after complete

recovery, such a state of things could still persist. Yet this old theory seems to me to contain a nucleus of truth, as is so often the case. The chief point of Chauveau's theory is that in the modified body the bacteria should not be able to assimilate certain food substances. Now, Chauveau's idea is that this could only take place if the substances in question were absent; this is obviously incorrect. But this hypothesis is not necessary in order to explain such insufficient nutrition of the bacteria; it suffices to assume that those substances may still be present, but that the parasitic agents in question are incapable of absorbing them; in other words, that the substances have ceased to be at the disposal of the bacteria.

This phenomenon, at the time of my cancer studies, I embodied in the definition of "Atrepsy." I will give you a few examples from my researches which will make clear what I mean by this definition, and I will begin with a fairly simple case, viz., that of the cobra venom.

This poison produces in the body a number of very different injuries, *e.g.*, it affects the nervous centres, the subcutaneous tissue, the red blood corpuscles, the endothelia, &c. But whilst the manifold pathological conditions produced in the body, *e.g.*, by corrosive sublimate or any other well-defined chemical substance, are in every case the effect of one substance on different organs—as, for instance, nephritis, inflammation of the salivary glands and necrosis of the intestinal mucosa are the result of the *one* poison, corrosive sublimate—the case is entirely different with snake venom, for there each separate and individual effect is the result of a different individual poison. Thus, one can prove with absolute certainty that the effect on the nervous tissues is produced by the neurotoxin, that on the blood corpuscles by a hæmolysine, and the inflammatory changes by a special endotheliotoxin. It has been shown that those components of snake venom which attack the red blood corpuscles are present in such a form that by themselves they do not suffice to destroy them.

By following up the researches of Flexner and Calmette, my former assistant and friend, Dr. Kyes, has succeeded in throwing some light on these difficult subjects. He proved that the hæmolytic component of the cobra venom is an amboceptor, which, however, differs from the bacteriolytic amboceptors in not combining with the complements of the blood, but which enters into union with a chemically well-defined substance, lecithin.

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By shaking cobra venom solutions with a solution of lecithin in chloroform, one can show that the whole hæmolytic toxin passes quantitatively into the chloroform, whilst the watery portion has retained the whole of the true poisonous principle, viz., the neurotoxin. From the chloroform solution one can isolate the active hæmolytic principle by precipitation with ether; it can thus be obtained in the form of a white powder, which, on chemical analysis, gives figures which almost exactly fit the formula of a mono-stearyl-lecithide. In this process there has, therefore, been split off one of the two molecules of fatty acid which can be recovered quantitatively from the ether.

The substance thus obtained is produced by the union of a small quantity of the hæmolytically active part of cobra venom with a relatively large number of lecithin molecules. It is easy to prove that in this we really have to do with a chemical compound, and not the result of an adsorption similar to that recently described by Michaelis between rennet and mastix; for it is impossible to split up the substance by solvents into two components, viz., monostearyl-lecithin and the cobra venom amboceptor, which should be possible if it were only such a mixture. On the other hand, in conformity with its altered chemical character, the substance has obtained new properties not found in cobra venom. For, in the first place, it is distinguished from the cobra amboceptor by having become so completely thermostable, that solutions of this cobra-lecithide can be boiled for hours without losing a fraction of their efficiency, whilst under similar conditions the original venom would be rapidly destroyed. A further important property is shown by the fact that cobra-lecithide, even in small quantity, instantaneously and without any incubation dissolves the erythrocytes, whilst snake venom, even in the presence of lecithin, only produces a similar effect after several hours. The long incubation period observed in experiments with the native poison is explained by the fact that the real poisonous body has first to be formed by a synthetic process, which, in dilute solutions and at ordinary temperatures, may naturally require some time for its completion. As you see, I believe with Kyes, that the hæmolysis of the red blood corpuscles is the result of a similar lecithid formation.

It is interesting to note the action of cobra venom towards different kinds of red blood corpuscles. It has been found that the corpuscles of the guinea-pig, man and rabbit, are at once dissolved

by solutions of the poison, but that this is not the case with sheep or ox corpuscles. These latter, however, are also dissolved if a small amount of lecithin is added to the mixture.

How is one to explain the fact that cobra venom cannot by itself dissolve certain kinds of blood?

It has been shown that in all bloods lecithin is present in fairly large quantities. If in spite of that only certain kinds of blood are affected by cobra venom, this must be explained by the assumption that in every blood lecithin is not present in the free state, but that it is combined with certain substances of the erythrocyte's stroma, and that the firmness of this union differs considerably in the different kinds of blood. That even in the resistant erythrocytes —*e.g.*, those of the sheep—lecithin is present as the activating substance, can easily be proved by breaking down the compound of proteid and lecithin. This can be done by extracting with alcohol. The alcoholic extract of sheep's blood corpuscles can be shown to activate a mixture of snake venom and sheep's corpuscles.

The results are different if, instead of cobra venom, other poisons are employed. Thus, the poison of *Bothrops lanceolatus* is absolutely unable to dissolve any of the above-mentioned bloods without the addition of lecithin, whilst the poison of *Trimesurus anamalensis* dissolves only the corpuscles of the guinea-pig, that of *Bungarus fasciatus* only the corpuscles of man and guinea-pigs, but not others. From these researches we may deduce two facts, viz.: (1) That the hæmolytic amboceptors of snake poisons possess different affinities for lecithin, this affinity being lowest in bothrops venom, which dissolves none of the before-mentioned corpuscles, and highest in cobra venom, which dissolves three of the five kinds; (2) that the firmness of union of the lecithin present in the different blood species is different, being highest in the sheep and the ox, lower in the rabbit, still lower in man and lowest of all in the guinea-pig. You see here very clearly one of the conditions which are of importance for the definition of atrepsy, namely, that of indisposibility. Lecithin has an affinity for certain constituents of the cell and it also has an affinity for the constituents of the poison; the difference between these two affinities decides whether cobra lecithid can be formed and hæmolysis can thus be produced. If the affinity of the constituents of the stromata is higher, hæmolysis does not take place, *i.e.*, the lecithin is not at the disposal of the cobra amboceptor.

I will now discuss a further similar case, namely, that of certain phenomena observed by me in the course of my studies on trypanosomes. As some of you may know, I have, together with my assistants, Dr. Röhl and Dr. Browning, proved that trypanosomes can be rendered resistant towards all those agents which may be employed for curative purposes. If, *e.g.*, a mouse infected with trypanosomes is treated with fuchsin, the parasites disappear, but return after a longer or shorter interval. If the treatment is then repeated, a similar result is observed. Thus this alternation of relapse and treatment can be repeated several times, though not indefinitely, for in course of time the effect of the fuchsin becomes more and more unsatisfactory and finally disappears altogether. If now the trypanosomes are transferred from such an animal to normal mice, these parasites are now, even in the normal mouse, found no longer capable of being influenced by fuchsin. There has thus been formed a "fuchsin-resistant" strain. I have chosen this expression because I found that a resistance once acquired, appears to remain unaltered even after as many as a hundred successive passages. We have up to now produced similar strains resistant to arsenical preparations, to trypan-red and trypan-blue as well as to fuchsin. In my next lecture I shall enter more fully into the importance of these strains.

I will here discuss one point only which is connected with to-day's subject, viz., the question as to the *origin* of the resistant strains. I have made the interesting observation on an arsenic-fast strain which was obtained by several years' treatment with atoxyl, and which was then made still more resistant by means of a very active arsenical preparation (No. 379), which I shall briefly call "Trypocid." This strain is distinguished from normal trypanosomes in that it is no longer influenced by this highly active arsenical preparation. One would have expected that also, in test-tube experiments, it would have shown a high resistance towards trypocid. Of course, such an examination could only be carried out by comparing it with other strains of trypanosomes. For obvious reasons I employed the original strain from which this resistant one had been derived, and which had been cultivated in the laboratory. I chose two animals containing about the same number of parasites and mixed their bloods with solutions of trypocid of different concentration. I now observed the very unexpected phenomenon that in these mixtures the immune strain

was far less resistant to higher doses of trypocid than the normal one. Thus whilst concentrations of 1 in 500 to 1 in 1,000 almost instantaneously killed the immune strain, the control strain retained its motility unimpaired in those concentrations for not less than five minutes.

We have here, therefore, one of those striking phenomena which have already been met with in the study of immunity and which consist in the simultaneous occurrence of immunity and hypersensibility in one and the same organism; but the case here is somewhat more simple, since we are working with a unicellular organism, and may therefore hope to obtain a more accurate idea of the case.

Allow me at this juncture to suggest to you a few fundamental principles. In order that a given poison, *e.g.*, the arsenical preparation, may act upon the trypanosomes, it must contain certain chemical groups which seize upon the latter. These groups I will distinguish from the ordinary receptors, which play an important part in the theory of immunity, by the name of chemo-receptors. In like manner the bodies of the higher animals must possess such chemo-receptors in certain organs, as they are also injured by the poison. If now a mouse infected with trypanosomes is injected with the arsenical medicament, this substance will be distributed between the parasites and the organism of the mouse. If the receptivity of the parasites is stronger, they will be killed in the organism; in the opposite case, they will not be destroyed. Consequently the curative result obtained when experimenting under normal circumstances represents also the differential between two avidities; *i.e.*, if a mouse infected with the normal strain of trypanosomes is injected with the arsenical preparation, the "trypanotropic" force of the drug is stronger than the "organotropic" force; we therefore obtain a curative effect with doses which are not injurious to the organism of the mouse.

In the resistant strains this is not the case, since the same doses show no trace of action on the parasites. One might imagine that this result was due to the trypanosomes having lost their chemo-receptors: but it is not necessary to make this assumption, and Nature has in its wonderfully complex mechanism found another and far more economical expedient than the loss of a perhaps necessary chemical structure. It is quite evident that the same result could be obtained if the chemo-receptors of the trypano-

somes were so far reduced in their affinity that the proportion of distribution was altered in favour of the chemo-receptors of the organism. That, indeed, is what takes place. Had the chemo-receptors quite disappeared, the immune strains would also in the test-tube experiment be more resistant than the normal ones; as a matter of fact, with certain preparations the contrary occurs.[1] The phenomenon is most easily explained by the supposition that the affinity of the chemo-receptors has become adjusted in such manner to the counterbalancing affinity of the mouse organism, that in the mouse no more arsenic remains at the disposal of the trypanosomes. If, however, this counterbalancing effect of the mouse's organism is removed, the poisonous agent can with full force seize the trypanosomes. I would even go so far as to say that we have to do in this case with a biological adjustment of the greatest delicacy, and that Nature limits herself to the most strictly necessary gradations and never allows a reduction of the affinity to its minimum.

As a proof of this I may mention a similar biological observation. I sent my resistant strain to the Liverpool School of Tropical Medicine, where it was found that the atoxyl-resistant strain showed the resistance as described by me only in mice but not in rats. This result was, of course, very surprising, but you will easily understand it on the basis of the previous results, by the supposition that the avidity of the rat's organism for trypocid is inferior to that of the mouse. In the rat, therefore, the trypanocidal effect is preponderant, since the trypanosomes are still able to seize upon the poison.

Let me now pass on to a very different field of research. I should be accused of carrying owls to Athens, if I were here to speak in detail of the nature and importance of Jenner's great discovery, which represents an epoch in our campaign against disease and the beginning of the period of immunisation. I shall

[1] The fact that these resistant strains are, in the test-tube experiment, affected even more severely than the normal ones, is the result of the co-existence of resistance and hyper-sensitivity in the parasite's protoplasm. Such a combination of immunity and hyper-sensitivity has repeatedly been observed in the course of the immunisation of higher animals, and is of late assuming increasing importance. It is the more interesting to note that the same phenomenon occurs also in uni-cellular organisms. The explanation of this observation will be given later.

therefore enter only into one question, which throws a little light upon that modification of the variola virus which is produced by its passage through the cow. As you know, animals are also affected with small-pox-like diseases which are closely related to human variola. Such diseases are the so-called "sheep-pox" and "bird-pox." The latter affection has recently been studied at my Institute by Dr. Sticker and Staff-Surgeon Marx. It is easily transferable by cutaneous inoculation to fowls and pigeons, and produces extensive small-pox-like hypertrophy of the epithelium. In the diseased epithelial cells highly staining spherical cell-inclusions are found, which must be identified with the corpuscles of Guarneri that are found in epithelial cells infected with small-pox or vaccine. Animals which have passed through the disease have acquired a complete immunity against subsequent infections.

As was shown by my assistants, the virus of bird-pox can be filtered through filter-candles. It can be transferred to fowls and pigeons. In fowls the virus retains its pathogenic properties unaltered for any number of inoculations. But the results are very different if one tries to inoculate with the diseased products occurring in pigeons. For although the inoculations can also be carried out in pigeons for any number of times, yet in such series the virulence for fowls has completely disappeared. You see, therefore, that we are here dealing with a process closely related to the modifications which the variola virus suffers in the organism of the cow. The only difference exists in the fact that in the one case the virulence for the original host is only reduced, whilst in the case of bird-pox it is completely destroyed. In my view this can be explained only in one way, for it is obviously impossible to suppose that by *one* passage through the pigeon's organism the parasites in question should obtain a new set of receptors capable of seizing upon antagonistic bodies present in the normal fowl's serum. It is far more natural to suppose that we have to do here with a form of atrepsy. It is safe to assume that the chemical composition of fowls' and pigeons' tissues is not identical, and that therefore the parasites, in their passage through the pigeon, must assimilate different substances to those assimilated in their passage through fowls. Therefore, that part of the receptors which deals with the nutritive substances in the fowl's organism is not in use during the passage through the pigeon. In view of their great instability it is possible that this portion of the receptors may become

atrophied, whilst the receptors specific for pigeon's substances become correspondingly increased. Thus the micro-organism would lose its power of assimilating certain substances of the fowl's organism. If such a parasite were transferred back to the fowl—supposing one of the specific constituents of fowls to be necessary for its proliferation—it would no more be able to grow in the fowl.

This is, therefore, a case of the loss of certain receptors which are absolutely necessary for nutrition. That such a change, having been once acquired, should be permanently transmitted from one generation to another, is hardly surprising in view of my recent observations on the modifications of arsenic-resistant trypanosomata. Obviously, the total loss of the chemical structures in question must render such modifications irreparable. Such characteristic instances as those in which a single passage produces a permanent loss of virulence for a certain animal species, are not very frequent. Correspondingly we may presume, that the variola virus when passing through the cow permanently loses certain atom-groups which cannot be regained; I believe, however, that in cow-pox this loss is of a lesser degree than in bird-pox.

On the other hand, in bacteriology we frequently find that such alterations produced by certain animal passages are not of a permanent nature. Thus one can, by successively passing streptococci through animals of one species, obtain a maximum of virulence for that species. It is possible, therefore, at will to produce a rabbit-strain, a mouse-strain, &c. But one can, by repeatedly passing such a strain through animals of a different species transform it into a different strain, and thus in course of time obtain from a rabbit-strain a mouse-strain. This is therefore a case of atrepsy of the receptoral apparatus of the bacteria for the animal species in question, but this atrepsy differs from that of the variations of small-pox by not possessing a permanent character.

Probably the majority of so-called non-pathogenic micro-organisms, if introduced into an animal's body, perish by this mechanism. It is not necessary to assume the presence of special poisons in the body, it suffices to suppose that the bacteria in question do not find the needful means of existence in the body and therefore cannot multiply. This being the case, they cannot for any length of time remain alive in the body, for then the latter's defensive forces, its phagocytes, come into action and destroy the invaders in a non-specific manner.

In the case of the pathogenic micro-organisms it will, however, as a general rule be wiser not to attribute too great an importance to atrepsy. But it is evident that micro-organisms can only be pathogenic for a certain animal if they find these possibilities of nutrition. Yet, to my mind, quite a number of infections are characterised by the fact that the micro-organism, with the exception of only a few remnants, becomes atreptic. As an example of such an occurrence I would mention the fine researches of my friend A. Neisser, who found that monkeys injected subcutaneously or intra-peritoneally with great quantities of syphilitic virus became neither infected nor immunised.

It does not appear possible to assume that in the serum of monkeys, substances should be present which destroy the causative agents of syphilis. It will be more correct to imagine that the delicate spirochætæ have lost their power of infecting because they have found no suitable nutritive bodies in the serum.

On the other hand we know, from the fundamental experiments of Metchnikoff and Roux, that typical primary lesions can in apes be obtained in any part of the skin, in the lower monkeys chiefly in the eyebrows and penis. Infection could also be produced by rubbing diseased tissue on to the cut surface of the testicle. On examining the inner organs of the monkeys Neisser found the virus to be present only in a few organs, especially the hæmatopoietic organs, viz., the spleen, the bone marrow and the lymphatic glands, as well as in the testicles, whilst all the other organs proved sterile. For this reason Neisser thought that the primary processes in certain defined tissues were of importance for the occurrence of the generalised disease. If we follow this view, it will be most easy to explain the state of affairs by the hypothesis that the serum of monkeys does not contain properties sufficient for the nutrition of the spirochætæ, whilst in certain cells of these animals, viz., the epithelia, the testicular cells and the leucogenic cells, substances permitting proliferation of the spirochætæ must be present. Probably there exists only a minimum of such a substance, auxiliary, but indispensable for their nutrition.

I may here remind you of the fact that the influenza bacillus, as was shown by R. Pfeiffer, is not able to proliferate in ordinary culture media, but that a trace of hæmoglobin is necessary for its growth. In syphilis I imagine the case to be somewhat similar. All the organs which can be primarily infected with

syphilitic virus would thus be the carriers of this specific auxiliary substance.

The case is more evident, macroscopically, in a great number of very different affections, *e.g.*, variola and vaccinia, bird's and sheep's pox, foot- and mouth-disease, trachoma, rabies, fowl's pest and scarlatina. In all these infections there are found in the epithelial cells the above-mentioned peculiar cell-inclusions, which in small-pox are called Guarneri's corpuscles, in rabies Negri's corpuscles. According to recent investigations we are justified in supposing that these inclusions do not themselves represent the parasites, but that they are derived from the cells and consist, according to von Prowazek, of plastin and nuclease. Within these masses there would lie enclosed the exceedingly minute disease-producing agents, these agents being in general so small as hardly to be accurately recognisable by the microscope, with the exception of the inclusions in trachoma, where the parasites are clearly visible and bear the stamp of something organised. We may safely assume that in all these cases the specific localisation of the parasites in certain distinct kinds of cells, points to the fact that in these cells, notably the epithelium cells in small-pox and trachoma, and the ganglion cells in rabies and fowl pest, such specific auxiliary bodies for the parasites are present, whilst in all the remaining parts the micro-organisms would encounter conditions of atrepsy.

The atreptic immunity, which results as I stated from certain substances not being at the disposal of the parasites, seems to me to play an important *rôle* in the study of tumours.

I may even say, that I first formed the idea of atrepsy as the result of numerous experimental observations upon malignant mouse tumours which are of cardinal interest for modern cancer research. I believe that a number of clinical and experimental facts in this sphere of knowledge can only be explained by this hypothesis.

As you know, mouse cancers are tumours showing a far-reaching analogy to human cancer, and it would therefore appear most justifiable to regard the experiences gained with them as the solid foundation of an experimental study of tumours. Besides several analogies, however, the mouse tumours show certain special features, chief among which is the mode of formation of metastases. It is most remarkable that the highly virulent carcinomata which have been cultivated in numerous generations, very rarely show

macroscopically visible metastases, whilst the slowly growing spontaneous tumours relatively more often, though also not very commonly, form large secondary nodules in the lungs. Our interest in this peculiar behaviour must even be increased, since Haaland has shown that microscopical metastases are by no means uncommon, but that they almost always remain below the limit of macroscopical visibility. I endeavoured to solve this problem by making, so to speak, artificial metastases, viz., by studying in animals affected with an inoculated tumour the result of a second inoculation. I found the interesting fact, that the effect of the second inoculation was inversely proportional to the energy of growth of the primary tumour. In rapidly growing sarcomata and carcinomata the second inoculation almost always had a negative result; at best, the second tumour remained far inferior in size to the primary one. Only in the very slowly growing chondromata was there no distinct difference in their energy of proliferation. These results agree with the following observation, which has been confirmed thousands of times. If, as is regularly done in my Institute, the inoculation is carried out by introducing the capillary tube at the groin and pushing it up as far as the axilla, the greater quantity of inoculated material will of course be deposited at the latter site, whilst only a small portion will remain at the groin. In the case of the rapidly growing carcinomata and sarcomata the large principal tumours almost always develop in the axilla, whilst a minute nodule is usually found in the groin. In the case of the chondromata, however, both tumours usually show a fairly equal development. Thus, in the latter case, the macroscopical appearance somewhat resembles that of an hour-glass, whilst in the former it is more like a balloon with its car attached to it.

To my mind, the explanation of this phenomenon is as follows: every proliferation depends in the first place on the avidity of the cells for the nutritive substances. Normally, there are certain well-defined laws of distribution, which guarantee the proper working of the organic functions. The avidity of the tumour cells is increased, compared with that of the body cells. The more energetically a tumour proliferates, the more vehemently does it attract the nutrient substances from the blood. In the case of a rapidly growing tumour it may therefore very easily occur, that for such cells which are under very unfavourable conditions of nutrition, *e.g.*, cells inoculated and metastatically carried away,

there is an insufficient supply of nutrient substances, and that they therefore either perish from atrepsy or at least are unfavourably influenced in their growth. From this point of view it is also quite evident that slowly growing tumours can attain far greater dimensions than rapidly growing ones, since in the former the consumption of nutrient matter, in spite of their size, is less than in the latter, and thus the entire organism is injured to a lesser extent.[1]

I fail to understand how von Dungern can think himself justified in doubting the correctness of this explanation, on the ground that hitherto the experimental proof of a permanent increase of cellular avidity by increased nutrition has not been adduced. I have never asserted that we can by artificial means permanently raise the cellular avidity. Such a power would obviously involve the possibility of artificial tumour production. There is therefore no contradiction, as von Dungern imagines, between my views and the facts that by artificial hyperæmia better nutrition is obtained, and that, after removal of large parts of the body, *e.g.*, amputation at the thigh, the hypernutrition of the individual is evidenced, not by the proliferation of functionating epithelial cells, but by increase of the paniculus adiposus. From the fact that the increased avidity causes an increased attraction of nutritive material, it does not follow inversely that copious nutrition should increase the avidity. An indirectly injurious effect of more highly avid cells on less avid ones can only, then, become evident, if the body does not possess sufficient nutrient matter to saturate every avidity. The origin of the higher avidity of the tumour cells is quite unknown to us; for this question means neither more nor less than the last problem of tumour ætiology.

An entirely different significance must be ascribed to the specific growth-stimulating bodies or "hormones," for the existence of which we have received irrefutable proof chiefly by the work of Starling. As you may know, he observed lactation in non-pregnant females as the result of injecting emulsions of embryos. But, of course, I should never think of asserting, as one might be led to think by von Dungern's explanation of my views, that as the

[1] In connection with this, attention may be called to the recent observations of Haaland (*Berl. Klin. Wochenschr.*, 1907, No. 23, p. 718), which show that pregnancy very often produces a retarding influence on the growth of such tumours.

result of over-nutrition a typical lactation might be set up in a virgin.

Such specific growth-stimulating bodies play an important *rôle* also in other cases, and are intimately connected with atreptic immunity. Thus we know that the influenza bacillus cannot do without hæmoglobin for its growth. Therefore it is quite easy to cultivate the bacillus directly from the sputum, which almost always contains small quantities of hæmoglobin. But if we do not artificially add hæmoglobin to the sub-cultures, the bacteria very soon die in them.

Specific auxiliary growth-substances we must also admit in all those infectious diseases which are characterised by a marked localisation of the poison, as in bird-pox and even syphilis.

The case is quite similar in that form of atreptic immunity which follows from my experiments of inoculating rats with tumour cells from mice. As you know, hitherto no one has ever succeeded in transferring normal or tumour tissue to animals of a different species. The limits of transplantability coincide with those of bastardisation. The question, however, now arose, as to whether the same barriers held good also for our highly virulent tumour material. To that end I employed the rat as the animal phylogenetically most nearly related to the mouse. In fact, if a virulent mouse tumour is inoculated into a rat, the result is quite different from all hitherto known true cases of transference of tissue outside a species; for during the first eight days the cells, both of carcinomata, sarcomata and chondromata, proliferate in the rat just as in the mouse. During this time tumours arise from the size of an almond to that of a date, containing numerous mitoses and even microscopically differing in no way from the mouse tumours. After that time, however, the limit of their growth is reached and there now follows gradual resorption, which is concluded after another week or two. If the tumour at its maximum development is transferred to another rat, it does not gain any foothold there, whilst if it is re-inoculated into a mouse it again proliferates luxuriantly. It is possible to keep on carrying out this zig-zag inoculation from mouse to rat and from rat to mouse, and again from mouse to rat, &c., for any length of time without the slightest check to the energy of proliferation being encountered. The question now arises, how it is possible to explain, on the basis of these facts, the immunity of the rat towards mouse-tumour cells.

We can at once exclude the existence of a natural immunity by antibodies in the rat, in view of the first luxuriant proliferation of the tumour. On the other hand it would be possible to imagine that the resorption of the tumour might be the result of an active immunisation of the rat. That such immunisation ultimately occurs may be proved by the fact that the result of re-inoculating a rat, in which a first tumour has been absorbed, with a second tumour, is always negative.

I do not, however, consider it permissible to identify these two manifestations of immunity. For in the first place it is highly improbable that, during the period of rapid proliferation of the tumour in the rat's organism, any considerable absorption of tissue elements should occur. Further, previous to that period a production of anti-bodies has not been proved. Lastly, since the tumour, when re-inoculated into the mouse, never shows ever so slight a reduction of virulence, one would have to suppose with von Dungern that the anti-substance formed in the rat's organism was activated only by the complements of rats but not of mice. This, again, has up to the present not been proved.

A far simpler and more natural explanation of all these phenomena is afforded by my hypothesis of atrepsy. According to this, the mouse-tumour cells require for their growth not only the ordinary nutritive substances which the rat can also supply to them in ample quantity, but, besides that, some well-defined substance which is present only in the mouse's organism.

In the rat, then, these cells would only be able to go on growing so long as there still remained to them some of the specific growth-stimulating substance that was introduced with them at the time of inoculation. When it has all been used up, growth can only be further stimulated by giving a fresh supply of this substance, *e.g.*, by re-inoculation into the mouse.

Just as it is impossible to explain this immunity of rats by anti-bodies, one cannot thus explain that form of immunity in mice which is evidenced by the differences observed in the number of positive results following inoculation with different tumour strains. Generally speaking, the proportion of positive results for one strain, with the exception of unavoidable chances, varies only within narrow limits. Thus, the strain of carcinoma which we cultivate in grey mice regularly grows in about 20 to 25 per cent.; Jensen's tumour, according to the publications, in about 40 to 60 per cent.,

our other carcinomata and sarcomata in 90 to 100 per cent., and our chondroma unexceptionally in 100 per cent. The constancy of these differences can never be explained by the assumption of anti-bodies, but only as the expression of a certain vitality of the tumour cells which is constant for each strain.

The atreptic condition is most clearly manifest in the cases repeatedly mentioned by Michaelis, Bashford and Haaland, where the transference to other races of mice of such virulent tumours was either quite impossible, or only succeeded in a very low percentage of cases. In the latter a gradual adaptation to the strange culture medium could only with great difficulty be obtained.

From my previous remarks it follows that the increased avidity of the cells for the food substances is the most important characteristic of the tumour cell. But this increase does not suffice to explain all the phenomena observed. Albrecht already insisted that for malignant tumours one must admit not only an increase but an alteration in the assimilation, in such manner that the "structure materials" taken up from the surrounding media must in some way be bound or laid up "until they had reached an amount sufficient for the division of the cell." Besides this increased food-absorption, the result of action of the receptors, chemiotactic remote effects must, to my mind, play an important *rôle*.

Such a phenomenon is very well shown by the chondroma which has been for many years cultivated in my Institute. This tumour shows a well-marked chemiotactic effect on the blood-vessels, in such manner that even small inoculated tumours, a week or two old, shine blue through the skin, whilst larger ones in their entirety present the appearance of a hæmorrhagic tumour. This angiotactic attraction of the blood-vessels is an essential condition for the growth of the tumours; for if, as is the case in intra-peritoneal inoculation, these angiotactic properties cannot become active, or if they have been lost, as is the case in immunised animals, proliferation remains very limited both as regards its duration and its extent, and it rapidly ceases whilst the whole tissue becomes necrotic.

As you see, I have dealt with a number of apparently very different subjects of biology and pathology, which are, however, united by a common bond. We have before us the competition of the different individualities for their nutrient materials. The majority of such chemical compounds are organically bound within

the cell to its constituents. This is, I think, especially true of the lipoid bodies, like fat, lecithin and others. In this respect I may, perhaps, remind you that normal tissue, *e.g.*, the cortex of the kidney, contains fat in such a hidden modification, since it shows fat granules neither microscopically nor by the osmic acid reaction. If one examines a similar organ in the stage of fatty degeneration, it shows macroscopically a white colour, and by microscopical examination with osmic acid shows an enormous number of fat granules. Yet, by extracting a normal and such a diseased kidney with ether and by examining the ether residue, Dunham showed that the quantities of extract thus obtained, which is but a mixture of fats and lecithin, is exactly the same in both cases. In this case, therefore, the occurrence of fatty degeneration consists only in the fact that the organic union between the proteids and the lipoids has ceased, and that the component parts have been liberated, and thus rendered easily recognisable.

These facts are completely analogous to the observations which I have previously communicated when discussing Kyes' researches on snake venom. I even think it probable that the sugars may, in a similar manner, be chemically firmly connected with the cells, and in like way the complex carbohydrates, *e.g.*, glycogen, may well be present in the body in a hidden form. That is at least made probable by an observation of mine on finding glycogen in the polynuclear cells, viz., that the normal polynuclear leucocytes never show the characteristic reaction with iodine, whilst it is frequently observed if some injury has befallen the body. Thus, as you are aware, in a number of intoxications the leucocytes give a positive glycogen reaction. Even the slightest stimuli may cause the leucocytes to split off glycogen in their protoplasm.

It will be necessary to assume that all these compounds are joined to certain protoplasmic groups, and that the decomposition of these compounds is the result of a fermentative action, resembling the decomposition of amygdalin, under the influence of emulsin, into glucose, hydrocyanic acid and benzaldehyde. Further, it is very interesting to note that one can often, by simply extracting substances like alcohol or ether, remove from the cells fat in the form of substances which still contain a protoplasmic component, although chemically they would appear at first sight to be pure lipoid substances. Such extracts have been prepared from red blood corpuscles by Landsteiner, Bang and Forssmann, who found

that by injecting such extracts into animals one can obtain specific hæmolysines. This phenomenon, which they endeavoured to use as an argument against my side-chain theory, is explained in the simplest manner by Kyes' observations upon the snake-venom lecithids. The lecithid would appear to be a pure fatty substance, being soluble in chloroform and even in toluol and alcohol, but as a matter of fact it contains, as I was before able to show you, a very slight quantity of the poison in chemical combination. And it is this portion which induces the biological reaction. The fact that, in spite of this component of a non-fatty nature, the compound apparently behaves like an ordinary fat, is due to the presence in it of a great number of fatty molecules which have given the whole substance its specific character.

I have frequently laid stress upon the fact that many nutrient substances are not present in the cells in a free state, and that, therefore, they are not at the disposal of any invader, but that a struggle is always necessary before they can be rendered accessible. In the case of snake venom I have shown that we are dealing with a simple difference between two chemical avidities. In the case of bacteria the affair may be rather more complicated, according to the occurrence of either of two possibilities, viz. : (1) A direct assimilation in consequence of a higher degree of affinity, or (2) an indirect action by injury to the cell. Supposing, for example, that a microbe had penetrated into a cell, but had not the power of directly splitting off the fatty bodies ; then these substances would not be immediately assimilable by it. Yet it would be able to obtain possession of them if it secreted a poison injurious to the cell, which would decompose the protoplasm. In such a case the fat would be liberated, and could be assimilated by the micro-organism, although the immediate affinity between the two might be a very low one. At any rate, these considerations may so far be of interest as they touch upon an issue of biology and pathology, which has, on the whole, been somewhat pushed into the background of late years, since one has accustomed oneself in every infective process to think in the first place of a specific bactericidal action through the direct toxic substances of the body, its haptines, &c. This has led to our neglecting somewhat the simple possibility that certain micro-organisms may only be able to grow if certain conditions are given for their development, and that they must perish if these conditions are withheld. To my mind this possi-

bility is of importance in many respects, and is especially significant for our views on cancer immunity. At any rate, we are dealing in these questions with a highly complex field of research, in which many possibilities are present, the most important being this difference of avidities.

We have previously seen that the trypanosomes may alter their avidity for arsenic, and thus acquire an apparent immunity. The contrary may occur in the case where the substance in question is not a poison, but a nutritive body. Here we should be perfectly justified in supposing the avidity of the receptor to have become increased. The same thing may take place with micro-organisms which can physiologically diminish or increase their avidities. Thus in all these cases the struggle lies between the adaptability of the parasite and that of the host. The one whose adaptability in the last place is the highest will remain the victor.

Of course this struggle is to a great extent influenced by indirect actions, consisting in the secretion by each antagonist of dissolved substances hostile to the vitality and receptivity of the other organism. On the part of the bacteria, these substances are the toxins and the dissolved intracellular substances; on the part of the body, the anti-substances.

A further *rôle* is played by actions of a protective and defensive nature. Thus we have shown that bacteria congregate in those parts where they find the most favourable conditions of nutrition, whilst the organism, both by its phagocytes and by means of encystment, endeavours to render the pathogenic germs harmless and to eliminate them. You see, therefore, that this is a war waged in different fields, but in which to every action there corresponds a reaction. The war is waged in a three-fold manner—by variations of affinity, by variations in the poison, and by localisation.

At the Reception given in honour of Professor Ehrlich at The Royal Institute of Public Health on the 6th June, Dr. L. Sambon exhibited a number of Linguatulidæ, worm-like arthropod parasites of snakes, two of which are parasites of man in their nymphal stage, a number of new larval tapeworms, and also some new Hæmogregarines, one of which he proposed to name *Hæmogregarina Ehrlichi* as a compliment to the distinguished visitor. This intention Professor Ehrlich was pleased to approve.

CHILD LIFE.[1]

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THE subject of my paper is so varied in its aspects, so important in its scope, so difficult in application and of such vital importance in its results, that the most I can do in the time at my disposal is to give you a panoramic view of the land of childhood, call your attention to some special features here and there, and then leave it to yourselves to revisit at leisure and make yourselves familiar with any spots that interest you directly or indirectly.

A well known poet has said that "The proper study of mankind is man," but if he lived in our days, when the search-lights of statistics—educational, medical and criminal—would throw some light into his study chamber, I think he would write "The proper study of mankind is the child."

What are children? They are men *in parvo*—the future citizens, who will conduct the throbbing social, commercial and political life of our great cities; the future parents, who will beget the future inhabitants of the land; the future magistrates, who will dispense justice; the future legislators and clergy, on whose integrity such mighty interests will in a great measure depend. Anything, then, that can help us to prepare them for the honourable acting of their parts on the stage of life is worthy of our deepest consideration.

Ordinarily speaking, childhood can be dealt with under two heads, viz., home life and school life, the latter being the indispensable complement of the former. This means that parents are primarily responsible for the training of the child, and that after a few years they are, not to hand over their precious charge entirely to the teacher, but to engage his services to supplement their efforts. Under their joint direction the child ought to be so equipped for the battle of life that the world will be the better for his advent, on account of the manner in which he orders all that concerns himself personally and all that brings him into contact with his fellow-men.

[1] A Paper read at the Cork Congress, 1906.